UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: ***Wave 4 Cases***	

GENERAL EXPERT REPORT OF KIM GEISINGER, M.D.

I. BACKGROUND AND QUALIFICATIONS

I am a licensed physician, board certified in Anatomic Pathology, Clinical Pathology, and Cytopathology. I am currently Professor of Pathology and Medical Director, Cytology Division, at the University of Mississippi Medical Center. Each year I personally interpret several thousand histopathologic specimens and several thousand cytologic samples. The majority of the latter are gynecologic in nature. I am licensed to practice medicine in North Carolina and Mississippi.

I earned my medical degree summa cum laude from the Medical College of Pennsylvania in 1976 and completed one year of cancer research at the same institution. Subsequently, I completed four years of postdoctoral training as a House Officer in the Department of Pathology at the University of Michigan in Ann Arbor, MI. Then, I completed a one-year fellowship in cytopathology at the Memorial Sloan-Kettering Cancer Center in New York City, NY.

I have served on the faculty of the Wake Forest University School of Medicine (where I was the Medical Director of both surgical pathology and of cytopathology for over two decades), and as an adjunct faculty member of the University of North Carolina School of Medicine. As a senior pathologist, I was involved in the morphologic interpretation of thousands of specimens annually, either as a primary pathologist or as a consultant pathologist. I have had the

opportunity to examine microscopically the human body's reaction to implanted foreign bodies, sutures, and a number of explanted mesh specimens. During my tenure at Wake Forest, I investigated and published manuscripts in peer review literature dealing with this research on various aspects of gynecologic diseases.

During my early years at Wake Forest, the institution had three gynecologic oncologists and two reproductive gynecologists. These individuals provided a wealth of gynecologic tissue and cytologic samples, which led to a number of publications dealing with this material. I became and am still an active member of the International Society of Gynecological Pathology. Over the years, I have given a number of national lectures related to women's health, especially dealing with gynecologic disorders; in fact, for about a five year period, I directed a course on women's health issues for the American Society of Clinical Pathology which was held in various cities in this country. Currently, I have several ongoing clinical research projects dealing with diseases of the uterine cervix; data from one of these was presented at the annual meeting of the American Society of Cytopathology in November 2016. I codirected a new endeavor: a health fair for indigent women in Jackson, MS that was held in January 2017, which included free pelvic examinations, Pap tests, and mammograms.

I have been involved in federally (US) funded research, with results published in peer reviewed literature, dealing with various aspects of patient safety issues, in particular those involving anatomic pathology; the principal investigator for these investigations was Dr. Stephen Raab, an individual with international recognition for such work. This work is ongoing.

Throughout my career, colleagues across the United States and in other countries (especially in Africa) have consulted with me on difficult or challenging specimens involving most body organs and tissues, including soft tissue and gynecologic samples.

As further detailed in my *curriculum vitae*, my work has been published in numerous peer reviewed journals, I have authored and/or edited several textbooks, and I frequently present at national and international meetings. I have been president of two national pathology organizations and served on a number of national and international medical committees.

My opinions that follow are held to a reasonable degree of medical and scientific certainty. Attached to this report are my curriculum vitae (Ex. A), which sets out my education and training in detail and lists my publications; a list of the materials I reviewed for this case and materials/exhibits which I will use to support my opinions (Ex. B); my fee schedule (Ex. C); and a list of deposition and trial testimony in the last four years (Ex. D). I expect to review the deposition transcripts of certain of plaintiffs' experts in this case and may further develop my opinions after having done so.

II. TISSUE RESPONSE TO IMPLANTED MATERIALS

Inflammation is a normal, required protective mechanism in animals including man which occurs in response to any number of stimuli that enter the body. Such agents include

bacteria, viruses, organ transplants, surgery of any type or degree including implantation of foreign bodies (e.g., sutures; hip replacement prostheses), cancers, and many unknown stimuli (e.g., the unknown cause of chronic ulcerative colitis). Inflammation may also occur when a normal organ undergoes changes in its antigenicity; this is referred to as autoimmune disorders. Small amounts of chronic inflammatory cells are not uncommonly found in tissues.

One basic medical concept of inflammation is that it is divided into two predominant forms: acute and chronic. There are two major sets of criteria for this division. The first of these is the type of inflammatory cell present or dominating in an area or focus of inflammation, as determined by microscopic exam. The classic cell for acute inflammation is the neutrophil. These cells normally are produced in the bone marrow and travel to the site of inflammation (regardless of the stimulus) via the bloodstream. Over time, often only a few days, neutrophils are replaced by chronic inflammatory cells. These include lymphocytes, plasma cells (a terminal form of lymphocyte that manufactures antibodies), monocytes, and macrophages (also termed histiocytes). These cells also travel via the blood to inflammatory sites, and gradually replace the neutrophils. In some instances, neutrophils persist with the chronic mononucleated cells for longer periods; this may be referred to as a mixed inflammatory reaction. Eosinophilic leukocytes are a peculiar inflammatory cell that may be associated with neutrophils in some circumstances and with chronic inflammatory cells in others. Some investigators refer to the process as subacute inflammation when eosinophils are plentiful. Eosinophils may predominate in allergic reactions, e.g., bronchial asthma.

The other guidepost for this division is the time interval from injurious stimulus to detection of disease. For example, if the skin is punctured, as by a knife during a traumatic event or by a scalpel used by a knowing surgeon, the injury is immediate and recognized as such (within short periods of time, neutrophils would be identified in the region of the puncture). It should be emphasized that essentially all forms of surgery incite an inflammatory reaction, regardless of whether or not they include the implantation of a foreign body such as mesh. On the other hand, for example, in some liver diseases, the disorder is not considered to be chronic unless it has been present for a minimum of six months. Chronicity, by itself, does not denote a worse or more troubling state.

A specific form of chronic inflammation is granulomatous inflammation. This picture histologically is generally dominated by macrophages which typically are derived from peripheral blood monocytes as they migrate into tissues. A granuloma may be defined as a rather well delineated collection of morphologically modified macrophages termed epithelioid cells. With varying frequency, some of the small mononucleated epithelioid cells fuse with one another forming multinucleated inflammatory giant cells. The classic granulomatous disease is tuberculosis. However, many other causes are recognized, such as dimorphic fungi, sarcoidosis and foreign bodies. In relation to the latter, granulomatous inflammation may be referred to as a foreign body reaction. Such reactions are truly expected adjacent to any implanted material, including biocompatible materials such as Prolene. As the reaction is expected, the presence of foreign body giant cells is not by itself a sign of lack of compatibility. Also often associated with granulomas are other chronic inflammatory cells, e.g., lymphocytes and plasma cells.

Occasionally, neutrophils are well represented in granulomatous disorders, as in cat scratch disease. Granulomas may or may not be associated with obvious tissue death (necrosis).

Directly associated with and following inflammatory processes is the proliferation of cells termed fibroblasts in granulation tissue, if there is a defect or deficiency of tissue. This is a key normal component of the body's healing or repair process. Fibroblasts are ubiquitous basic mesenchymal cells which migrate to and proliferate in such defects. One of their major functions is the production of and the extracellular deposition of collagen. Collagen is a family of proteins that provide structural integrity and strength to the body. Granulation tissue is a combination of fibroblasts, immature endothelial cells (angioblasts) that will form the inner lining of blood vessels, immature collagen (generally type III) and extracellular matrix of mucopolysacchrides. Granulation tissue itself is somewhat disordered and does not confer great binding strength to tissues. With time, the granulation tissue will evolve to progressively more mature fibrous connective tissue characterized by far fewer cells, less vasculature, far more collagen deposition, and conversion to the strongest type of collagen (type I). This is recognized clinically and microscopically as dense collagenous tissue, which is an expected, crucial component of healing from most surgeries of almost any type.

Tissue Ingrowth

In 1997, Dr. Amid, published a widely used classification of materials used for hernia repairs using mesh materials. This classification divided such materials into four categories based on several factors: structure (mono- vs multifilament), pore size (micro vs macroporous), composition (biologic vs synthetic) and arrangement (woven vs knitted). Type one (macroporous mesh with pores greater than 75 microns) mesh is considered sufficient to permit entry of inflammatory cells and other necessary cell types. Type one mesh is composed of polypropylene that is macroporous and monofilament. The macroporous mesh allows all cells involved in inflammation and repair to enter the interstices of the mess material. In addition to facilitating stability of the mesh within the surrounding tissues, it reduces greatly the risk of infection. Bacteria are much smaller than these human cells and may readily enter the pores of mesh with micropores; however, these pores are too small to permit entry of inflammatory cells which the body depends on to help eradicate many infections. The monofilament nature is also of value here as it does not possess interfilament crevices in which bacteria could enter and "hide" from inflammatory cells which would likely be able to reach the microorganisms. Peri- and postoperative infection is a well-recognized complication of surgery which leads to significant morbidity and mortality. It also is a leading cause of prolonged hospital stays and expenses to the medical ecosystem. The macroporous meshes allow the migration of fibroblasts into the mesh, permitting the creation of the expected and needed fibrosis. Also important, it permits the entry of endothelial cells to develop intramesh tissue vascularity to provide good blood vessel development, vital to maintaining the health of healed tissues. One additional benefit of the macroporous mesh is that it markedly reduces the likelihood of the evolution of a significant scar capsule which consists of an encircling of much of or the entire graft by collagen rich scar tissue.

Wound Healing

A number of clinical factors play roles in the ability to impact the rate and success of wound healing. A partial list includes: poor nutrition pre- and perioperatively, pre-existing cardiovascular disease which may act to deprive oxygen and nutrients to the healing site, diabetes mellitus (and possibly related obesity), renal or cardiovascular disease which accentuates edema in the wound site, cigarette smoking, prior exposure to radiation, and poor collagen formation. In addition, data shows that patients with high levels of preoperative distress or anxiety heal more slowly; this may be modulated at least in part via the body's immune system (Kiecott-Glaser, American Psychologist 1998; 53: 1209-18). Finally, healing depends to an extent on the experiences and skills of the surgeon.

Correlations

In the presence of sufficient scientifically reliable evidence, practicing anatomic pathologists correlate gross pathologic and especially microscopic (histopathologic) attributes of a patient's specimen with known demographic and clinical data of that specific patient. In addition, this morphologic assessment may be utilized to predict, along with clinical factors, the prognosis of a patient if there is a sufficient basis in the scientific knowledge. Furthermore, it may be used to help determine what therapy to provide and how the patient may respond to a given regimen. However, this is not possible where the scientific evidence has not established histologic features that are predictive of symptomatology.

Classic clinicopathologic correlations, which are done numerous times a day in this country, include integrating clinical data with the pathologic findings, supported by tested scientific evidence. In a number of instances, this utilizes special testing such as immunohistochemistry, and conferring with the appropriate clinicians. All of this is founded on evidence based medicine in which facts or at least strong correlations support certain medical thoughts and actions. Hypotheses are not sufficient to draw a correlation.

This classic correlation does not entail attempting to propose that specific symptoms or disease manifestations are related to microscopic findings, including attempting to explain the complex symptom of pain based on what is seen with the microscope. In the 30 years of my career, I have never been asked by a clinical colleague whether the presence of nerves in the histologic sections of a specimen that might explain the patient's pain. Similarly, I have never stated such in a specimen report. This is also true of lesions in which pain is well recognized by data to be associated, e.g., traumatic neuromas and angiolipomas. This is not the role of a pathologist, particularly as regards pain because pain is a complex symptom that cannot be reduced to the appearance of tissue under the microscope. Regarding explanted meshes, there is no evidence base in the scientific literature that would support a trained pathologist to correlate histologic findings with symptoms. In fact, Hill in 2015 attempted to do so and found no difference in inflammation and fibrosis between painful vs non-painful stress urinary incontinence mesh slings. Klosterhalfen in 2002 reported similar findings regard hernia meshes as regards inflammation.

The presence histologically of neural tissue does not mean those nerves are capable of transmitting pain signals. Some neurons are motor in type, others are sensory, and still some are

associated with the autonomic nervous system. Thus, some are involved with movement of specific body parts, others with the delivery of sensory stimuli (pain, pressure, touch, etc.) to more central parts of the nervous system, and still others with processes such as sweating or blushing. In general, a pathologist cannot look at neural tissue histologically and determine the nerve type present. Thus, to state that pain is related to neural tissue in sections is fully speculative, and not based on fact or well recognized knowledge.

III. HISTOLOGY OF EXPLANTED MESH

Ethicon's Prolene has been used as a suture for decades. The company began using Prolene as a mesh material first in hernia applications and then later to treat stress urinary incontinence. Prolene, as a monofilament mesh with a pore size of 1379 microns, is considered an Amid Type 1 macroporous mesh. (Moalli, 2008 Int Urogynecol J; 19:655-63). Ethicon eventually developed a wider pore mesh for the treatment of pelvic organ prolapse using Prolene Soft mesh, which is also a monofilament, Type 1 macroporous mesh with a different pore than those in Prolene. (Jones, 2009 Int Urogynecol J; 20:847-53). As discussed below, the tissue reaction seen to both Prolene used in Ethicon's TVT products and to Prolene Soft used in Ethicon's pelvic organ prolapse products (e.g., Gynemesh PS, Prolift, and Prosima) is an expected, non-troubling foreign body reaction that leads to good tissue ingrowth. This tissue ingrowth is necessary for the stability of the repair.

I have reviewed a number of surgical pathology specimens from the vagina and perivaginal tissues containing Prolene based meshes that were supplied to me by Butler Snow. My findings and experiences are consistent with the published literature regarding the tissue reaction to Prolene based meshes used to treat stress urinary incontinence and pelvic organ prolapse. Most of the explanted meshes that I recently reviewed consisted of one or two blocks, with one or more hematoxylin and eosin stained sections from each block. A minority of the samples had one or more immunohistochemical reactions as well; most commonly these were for S100 protein. I looked at each without any clinical data, e.g. patient age, length of implant before removal. I utilized the histologic scoring system recently published by Hill et al.

Overall, I witnessed what I interpreted as a grade 1 degree of inflammation. Frequently, this consisted of macrophages with or without giant cells and infrequent lymphocytes. In such, the histiocytes appeared to be physically closer and often in direct contact with the filaments. Conversely, the lymphocytes were more peripherally associated. Infrequently, a mild lymphoplasmacytic response was dominant. Neutrophils were rare except in instances of what I interpreted as disruption of the vaginal epithelium.

My general impression was that the fibrosis occurred to a greater extent than the inflammation and gave it an overall score of two (Hill). Fibrosis filling the pore space was only focally and occasionally noted. I did not see what I thought of as encapsulation.

In specimens with what appeared to be vaginal epithelial defects, the subepithelial lamina propria was either inflamed with a lymphoplasmacytic infiltrate and/or granulation tissue. At times, neutrophils infiltrated the epithelium. In those sections in which filaments were present, they differed from those more firmly surrounded by connective tissue. They appeared isolated or

loose in the tissues and not associated with an attached foreign body reaction. The reaction seen in these specimens is expected given that the mucosa has been disrupted and the mesh and underlying tissue have been exposed to the outside world.

Concerning the immunohistochemical stains, the S100 protein stains neural tissue. Not infrequently, this appears to be pre-existing nerves due to their normal appearance. At other foci, they appear as nerve "twigs" which I would define here as single staining fibers or perhaps two immediately adjacent fibers. They have a high length to width ratio and a slightly wavy contour. Other structures are also positive with this reaction which may well not be neural; rather, they may be dendritic reticulum cells, related to histiocytes. They have a lower length to width ratio and resemble somewhat "sausages." I did not see anything that I would say closely resembled a traumatic neuroma. In my opinion, the neurofilament stain did not coincide with the S100 protein stain, casting some doubt on the neural nature of some of these cellular elements.

Kelley et al reviewed publications dealing with several different aspects of synthetic mesh materials implanted in animal models. For example, Harrell and colleagues examined and compared four mesh products implanted into rabbits for four months; histologically, less inflammation was associated with polypropylene than with the other materials. Huffaker et al also studied mesh in rabbits, including Prolene Soft. Polypropylene was compared with sham (no mesh) operations. Of course, compared to sham surgery sites, polypropylene had higher inflammatory and fibrosis scores (using their scoring system); however, still in the mesh sites, the inflammatory scores were mild and the fibrosis scores were minimal. Good tissue incorporation was noted. In addition to routine histology, these authors evaluated special tissue techniques to evaluate cellular proliferation and apoptosis at the tissue-mesh interface. Usually, both were low.

Hutchinson and colleagues examined polypropylene mesh implanted subcutaneously in rats over a 91 day period; they reported minimal to mild fibrosis, with mostly mild fibrosis scores at the end of 91 days with Prolene and Prolene Soft mesh. From their published photomicrographs, the inflammatory reaction also appeared mild; it consisted largely of histiocytes with scattered lymphocytes. Using Prolene and other mesh types in a porcine model, Boulanger et al reported a mild lymphohistiocytic reaction at well integrated tissue mesh interfaces. The tissues were described as well vascularized and possessing well organized collagen-rich connective tissues.

The data from the review of Kelly indicated that the large pore size in polypropylene meshes, compared to most other products, allowed for the integration of the mesh into the tissue to be optimized with an ingrowth of fibroblasts and angioblasts. Furthermore, if infectious agents were present, the larger pore size permitted the defensive infiltration of inflammatory cells to ameliorate the process.

Histopathologic studies exist examining human tissue following surgery in which mesh and its interactions with host tissues are evaluated. A limitation in some of these investigations is the lack of correlation with symptomology and clinical attributes. These include patients with hernia repairs and with surgery for POP. It is fair to state that the vast majority of the published data demonstrate the excellent qualities of polypropylene mesh in these clinical scenarios For

example, Woodruff et al compared 24 explanted slings composed of several different mesh materials. With polypropylene, relatively large numbers of fibroblasts were able to infiltrate the mesh along with a moderate degree of neovascularization. Consequently, there was no evidence of graft degradation, encapsulation of infection.

Elmer and colleagues microscopically compared vaginal punch biopsies from ten women with Prolift mesh to treat pelvic organ prolapse and 8 controls (no mesh). Each patient had two biopsies obtained, one preoperatively and one at a year following surgery. The foreign body inflammatory reaction was quantitated with both routine histology and using a computer image based system. The mesh stimulated a mild and persistent increase in the number of macrophages, but not an increase in plasma cells, lymphocytes and neutrophils. At one year postoperatively, they claimed the healing process was complete with reduced numbers of fibroblasts. No significant change was detected for either the collagen density or the content of elastic fibers. Falconer et al also utilized punch biopsies; they targeted periurethral tissues at the time of surgery and two years postoperatively. In women with Prolene mesh, there was no minimal inflammation or fibrosis in the subepithelial stroma, while there was a significant inflammatory reaction seen in patients where Mersilene mesh had been used.

Hill et al have provided, in my opinion, the single most quantitative histomorphologic analysis to date. They developed microscopic scoring systems for the degrees of inflammation and of fibrosis. Furthermore, their investigation did attempt to correlate clinical symptoms in women with midurethral slings with the histologic attributes. According to symptoms, the women were divided into three groups: Group one were patients who presented with voiding dysfunction only, Group 2 were those with only pain and Group 3 were those with both pain and voiding dysfunction. For patients with polypropylene mesh slings, the Group 1 patients had higher inflammation and similar fibrosis scores compared to those in Groups 2 and 3. No positive correlation was found between inflammation and/or fibrosis and pain. Their description of the histology of inflammation and fibrosis parallel my microscopic experiences.

Smith et al concluded that, in clinical practice, the microscopic examination of mesh and the associated tissues were generally not necessary.

In sum, the published data and my own experience shows that both Prolene (as used in Ethicon's TVT devices) and Prolene Soft meshes (e.g., as used in Gynecare's Prolift) induce a minimal to mild chronic inflammatory infiltrate, with mild to moderate fibrosis. A foreign body reaction often surrounds the mesh fibers as well, but is limited to the tissue adjacent to mesh fibers. These macroporous meshes exhibit adequate tissue integration and vascularization of the tissue, with no encapsulation by scar tissue. The adequate pore sizes of Prolene used in Ethicon's slings and Prolene Soft used in its pelvic organ prolapse meshes also allow for the body's immune response to clear bacteria. There is nothing about these findings that can be correlated by any pathologist with the symptomatology of pain, as demonstrated by both Hill and Klosterhalfen.

IV. RESPONSE TO DR. VLADIMIR IAKOVLEV'S OPINIONS

I have reviewed Dr. Iakovlev's general report and have the following opinions on his findings and conclusions.

In his expert report dated January 29, 2016, he states on the very first page that as a physician, he works to "reach conclusions about the cause of a patient's illness or injury." This is a most exceptional statement by a pathologist. I take difference with the term "cause." Pathologists generally do not render causes in their official written reports or in less formal communications with treating physicians. As explained previously, in the context of resected vaginal mesh, there is insufficient scientific evidence to draw conclusions about symptoms a patient experiences from histologic findings.

Also in his report, on page 2, he states that some research publications show "pathological mechanisms in patient samples;" he then cites his own publications. I disagree. The authors of these manuscripts describe the histomorphology of portions of specimens (e.g., the degree of fibrosis and the proliferation of neural tissue). Yes, they are delineated, but there is no substantial proof that these static pathologic changes are mechanistic; it is all speculative. Histology does not demonstrate or correlate well with pathogenesis. This lack of pathogenetic proof of scar, mesh folding, nerve growth, etc. are described in his publications as causative but there is no real proof. In fact, two of his publications somewhat refute each other on this. Both investigated nerve density and its association with clinical pain in patients. One said yes; the other said no. Both publications have the lead author as Dr. Bendavid (Hernia 2015; and Intern J Clin Med 2014; 5: 799-810). Throughout his opinion, Dr. Iakovlev inappropriately attributes various histological findings with pain (e.g., inflammation, scar, presence of nerves, etc.). As discussed above, there is no scientific evidence available to support these theories regarding polypropylene mesh, as the most robust study looking at the issue has not found histological correlates in explanted meshes to explain pain. Without evidence based on comparators, Dr. Iakovlev's attempts to correlate symptoms with histology are speculation.

In the section Mesh Integration, he states that mammalian connective tissue does not regenerate. This is not correct. In fact, he discusses in several places granulation tissue. This is a regenerating connective tissue. Fibroblasts are clearly of mesenchymal origin and in granulation tissue are clearly growing. This is what mesenchymal repair is all about.

Dr. Iakovlev's report includes a section on polypropylene degradation and then includes photomicrographs showing a rim of material around mesh fibers that stains using histological dyes. What Dr. Iakovlev presents is merely a hypothesis based on visual observation unless he is able to identify that the rim of material (his "bark") consists of degraded polypropylene through chemical means. He then must demonstrate through science, not conjecture, that the "bark" is a result of degradation *in vivo* rather than an artifact from the surgical manipulation, fixation, processing, and microtomy that occurs with explanted tissue and mesh prior to review under the microscope. Because Dr. Iakovlev has not done this, his opinion is speculation.

Number 15 of his summary opinions states that curled and folded mesh is stiffer and has a greater likelihood of cutting tissue than flat mesh. He provides no data to support this and cites no references. Moreover, it is improper for Dr. Iakovlev to extrapolate the in vivo, three-

dimensional conformation of mesh fibers from formalin fixed paraffin embedded tissues. Resection, fixation, and processing are known to shrink tissues. Moreover, explanted mesh specimens are sufficiently "changed" by the time they reach the pathology laboratory, and certainly by the time they are on a slide, for any pathology to assess contraction/shrinkage, deformation/curling, or stiffening. As stated above, no attempt has been made by Dr. Iakovlev to provide evidence to permit a correlation between such conformational changes (if they exist) and symptoms.

Dr. Iakovlev includes an opinion on mesh migration. Pathologists review tissue under the microscope and see only an image at one point in time. This does not permit conclusions to be made about the movement or lack of movement of the mesh.

In several sections of his report, he claims that traumatic neuromas and "nerve deformation" are present histologically. These images do not demonstrate in my opinion the neural proliferation required in traumatic neuromas. Traumatic neuromas are usually described as a palpable mass or nodule that may be associated with pain and most commonly are associated with limb amputations. Clearly, the small aggregates he refers to as neuromas are not palpable and thus lack the mass needed for a neuroma. With regard to "deformed" nerves, Dr. Iakovlev glosses over the fact that nerve fibers in formalin fixed paraffin embedded tissue are often artifactually distorted by the processing and fixation alone. Again, Dr. Iakovlev provides no evidence that any of the histological appearances of nerves correlate with symptoms.

In Figure set 5 in his report and the associated text, he describes a large increase in nerves in the vaginal mucosa. The mucosa of this organ has two parts: epithelium and lamina propria. The normal lamina propria normally has a goodly nerve supply. His S100 protein immunostain does not show, in my opinion, an increase above normal. In fact, I think some of the positive cells here are not neural in type but rather dendritic cells related to macrophages which are also normally present in this location. Further, nerve cells are not normally present in the vaginal epithelium. I do not believe his image shows such; rather, it demonstrates intraepithelial Langerhans cells, a form of antigen delivering histiocyte.

V. CONCLUSIONS

1. Following the implantation of any medical device, the body's response includes acute inflammation that transitions to chronic inflammation and a foreign body response. The presence of chronic inflammation and foreign body response is expected.

2. Fibrosis is a normal component of the healing process. Without it, implanted mesh would not provide the supportive function necessary to treat stress urinary incontinence and pelvic organ prolapse.

3. Both of these normal processes, inflammation and fibrosis, occur in association with all surgical procedures, including implantation of foreign bodies such as Prolene and Prolene Soft based mesh.

4. As Type 1 macroporous meshes, Prolene and Prolene Soft meshes are associated with a minimal to mild chronic inflammatory response and a mild to moderate degree of fibrosis. Comprehensive reviews, such as done by Kelly and colleagues, demonstrate that polypropylene (including Prolene and Prolene Soft) elicits less of an inflammatory response than other materials. My review of meshes explanted from women confirms the above findings described in the literature.

5. With perhaps the exception of localized pain during an active exposure or erosion of mesh, where the vaginal mucosal is disrupted, there is currently no reliable scientific evidence that would permit a pathologist to correlate histologic findings from explanted mesh with patients' symptoms. Both Hill and Klosterhalfen have demonstrated that this cannot currently be done.

DATED: FEBRUARY 16, 2017

Kim Geisinger, M.D.